Complete Summary

GUIDELINE TITLE

Menopause and hormone therapy (HT): collaborative decision-making and management.

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Menopause and hormone therapy (HT): collaborative decision-making and management. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2005 Aug. 64 p. [176 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Institute for Clinical Systems Improvement (ICSI). Menopause and hormone therapy (HT): collaborative decision-making and management. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2004 Oct. 57 p.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- On May 12, 2006, GlaxoSmithKline (GSK) and the U.S. Food and Drug Administration (FDA) notified healthcare professionals of changes to the Clinical Worsening and Suicide Risk subsection of the WARNINGS section in the prescribing Information for Paxil and Paxil CR. These labeling changes relate to adult patients, particularly those who are younger adults.

  A recent meta-analysis conducted of suicidal behavior and ideation in placebo-controlled clinical trials of paroxetine in adult patients with psychiatric disorders including Major Depressive Disorder (MDD), other depression and non-depression disorders. Results of this analysis showed a higher frequency of suicidal behavior in young adults treated with paroxetine compared with placebo. Further, in the analysis of adults with MDD (all ages), the frequency of suicidal behavior was higher in patients treated with paroxetine compared with placebo. This difference was statistically significant; however, as the absolute number and incidence of events are small, these data should be interpreted with caution. All of the reported events of suicidal behavior in the

adult patients with MDD were non-fatal suicide attempts, and the majority of these attempts (8 of 11) were in younger adults aged 18-30. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

It is important that all patients, especially young adults and those who are improving, receive careful monitoring during paroxetine therapy regardless of the condition being treated. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Menopause and perimenopause

GUIDELINE CATEGORY

Counseling
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations

Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To outline a process for effective collaborative decision-making regarding both treatment and prevention strategies
- To increase the percentage of perimenopausal/menopausal women who receive education describing risk and benefits of hormone therapy (HT)
- To increase the percentage of women with appropriate follow-up to cessation of HT

TARGET POPULATION

- All women interested in discussing midlife health issues
- Perimenopausal women with menopausal symptoms
- Women currently or recently using hormone therapy

INTERVENTIONS AND PRACTICES CONSIDERED

Counseling/Management

1. Discussion of midlife health issues and menopause with patient: healthy lifestyle, subtle signs of menopause, current menopausal status, and counseling and education strategies
2. Discussion of menopausal symptoms and risks/benefits of therapy options, including lifestyle modifications and hormone therapy (HT)
3. Assessment and discussion of disease prevention, including osteoporosis, coronary heart disease (CHD), Alzheimer's disease, colorectal cancer, skin/wound healing, tooth loss, and macular degeneration and limited role of HT
4. Evaluation of patient conditions for which HT might be indicated or contraindicated
5. Clarification/discussion of patient's values and priorities regarding treatment of menopausal symptoms
6. Formulation of treatment plan
7. Evaluation (including endometrial assessment) and management of side effects
8. Follow-up after decision to initiate HT

Treatment

1. Initiating HT
    - Consideration of estrogen-progestin combination vs. estrogen-only HT
    - Patient education on bleeding patterns and possible side effects
2. Modifying HT in long-term users
3. Discontinuing HT in long-term users
4. Evaluate and manage side effects
5. Follow up

Note: This guideline does not endorse or recommend herbal remedies for menopause-related symptoms, but does include a list of non-FDA approved products, including selected herbal preparations, as a guide for clinicians.

MAJOR OUTCOMES CONSIDERED

- Patient satisfaction
- Effects of hormone therapy (HT) and other therapies on menopausal symptoms, bone mineral density, and fractures
- Risks of developing breast cancer, endometrial cancer, gallbladder disease, venous thromboembolism, or ovarian cancer with HT
- Effects of HT on cardiovascular health
- Effects of HT on Alzheimer's disease, colorectal cancer, skin/wound healing, tooth loss, and macular degeneration
- Adverse effects and complications of HT

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system presented below, and are designated as positive, negative, or neutral to reflect the study quality.

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Study Quality Designations

The quality of the primary research reports and systematic reviews are designated in the following ways on the conclusion grading worksheets:

Positive: indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis.

Negative: indicates that these issues (inclusion/exclusion, bias, generalizability, and data collection and analysis) have not been adequately addressed.

Neutral: indicates that the report or review is neither exceptionally strong nor exceptionally weak.

Not Applicable: indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Nonrandomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Clinical Validation-Pilot Testing
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Institute Partners: System-Wide Review

The guideline annotation, discussion, and measurement specification documents undergo thorough review. Written comments are solicited from clinical, measurement, and management experts from within the member groups during an eight-week review period.

Each of the Institute's participating member groups determines its own process for distributing the guideline and obtaining feedback. Clinicians are asked to suggest modifications based on their understanding of the clinical literature coupled with their clinical expertise. Representatives from all departments involved in implementation and measurement review the guideline to determine its operational impact. Measurement specifications for selected measures are developed by the Institute for Clinical Systems Improvement (ICSI) in collaboration with participating member groups following implementation of the guideline. The specifications suggest approaches to operationalizing the measure.

Guideline Work Group

Following the completion of the review period, the guideline work group meets 1 to 2 times to review the input received. The original guideline is revised as necessary, and a written response is prepared to address each of the responses received from member groups. Two members of the Ob/Gyn Steering Committee carefully review the input, the work group responses, and the revised draft of the guideline. They report to the entire committee their assessment of four questions: (1) Is there consensus among all ICSI member groups and hospitals on the content of the guideline document? (2) Has the drafting work group answered all criticisms reasonably from the member groups? (3) Within the knowledge of the appointed reviewer, is the evidence cited in the document current and not out-of-date? (4) Is the document sufficiently similar to the prior edition that a more thorough review (critical review) is not needed by the member group? The committee then either approves the guideline for release as submitted or negotiates changes with the work group representative present at the meeting.

Pilot Test

Member groups may introduce the guideline at pilot sites, providing training to the clinical staff and incorporating it into the organization's scheduling, computer, and other practice systems. Evaluation and assessment occur throughout the pilot test phase, which usually lasts for three to six months. At the end of the pilot test phase, ICSI staff and the leader of the work group conduct an interview with the member groups participating in the pilot test phase to review their experience and gather comments, suggestions, and implementation tools.

The guideline work group meets to review the pilot sites' experiences and makes the necessary revisions to the guideline, and the Ob/Gyn Steering Committee reviews the revised guideline and approves it for release.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC) and the Institute for Clinical Systems Improvement (ICSI): In addition to updating their clinical guidance, ICSI has developed a new format for all guidelines. Key additions and changes include: combination of the annotation and discussion section; the addition of "Key Points" at the beginning of most annotations; the inclusion of references supporting the recommendations; and a complete list of references in the Supporting Evidence section of the guideline. For a description of what has changed since the previous version of this guidance, refer to Summary of Changes - August 2005.

Menopause and Hormone Therapy (HT): Collaborative Decision Making and Management

The recommendations for menopause and hormone therapy (HT) are presented in the form of an algorithm. An algorithm is provided for Menopause and Hormone Therapy (HT): Collaborative Decision-Making and Management with 8 components, accompanied by detailed annotations. Clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Class of evidence (A-D, M, R, X) and conclusion grade (I-III, Not Assignable) definitions are provided at the end of the "Major Recommendations" field.

Clinical Highlights

1. There are many effective options to be considered for the relief of menopausal symptoms; although hormone therapy (HT) is often the most effective treatment, it is not always necessary. (Annotation #2a)
2. Periodically re-evaluate women on HT to determine if it is still indicated, particularly if there have been changes in their health status. (Annotations #2b, 7)
3. Women who have recently discontinued HT are at risk for rapid bone loss; they must be identified and monitored appropriately to ensure continued bone health. (Annotations #2b, 2c)
4. At this time, the role of HT in disease prevention has been all but eliminated in current practice. (Annotation #2c)
5. The well-publicized results of several recent clinical trials have resulted in increased apprehension about HT among both patients and providers. It is unlikely that definitive information or consensus will be available anytime soon. (Annotations #1, 3)
6. The exact risks associated with HT, as well as possible side effects, may not be fully defined, but they cannot be dismissed and must always be considered and discussed as part of the collaborative decision-making process. (Annotations #3, 4, 6a)

7. Careful consideration and in-depth discussion are required whenever the initiation or continuation of HT is considered; help each woman clarify her individual values and priorities so that she may decide how important each of the potential benefits and risks of HT is to her unique situation. (Annotation #4)
8. Provide support and encouragement, through accessibility and close follow-up, for women who have recently initiated HT. (Annotations #6a, 7, 8)

Menopause and Hormone Therapy (HT): Collaborative Decision-Making and Management Algorithm Annotations

1. Discuss Midlife Health Issues and Menopause

   Key Points:

   - Consider initiating discussions about menopause and HT starting at age 40.
   - Be alert to subtle signs of menopause, including mood and sleep disturbances.
   - Laboratory testing is usually not necessary to establish menopausal status.
   - In counseling patients, distinguish between short-term hormone therapy for menopausal symptom relief (minimal risk) and long-term hormone therapy for the prevention of chronic disease (rarely initiated).

   Consider initiating a discussion about these issues as part of routine health maintenance visits with women 40 years of age or older. Many women wish to begin this discussion well before menopause.

   For women on HT, regularly review and discuss its use. (See also Annotation #2b, "Discuss Options for Long-Term HT Users; Ensure Continued Bone Health".)

   There are three distinct areas for discussion and decision-making related to midlife health issues. These are reflected in the organization of this guideline:

   - Options for menopausal symptom relief
   - Options for women who have been long-term HT users and who seek advice about continuing, stopping, or modifying their regimen
   - Options for risk factor modification and disease prevention

   Encourage healthy lifestyles

   Always emphasize healthy lifestyles and lifestyle modifications as the most important first step in both menopausal symptom relief and disease prevention.

   Clarify Menopausal status; be alert to subtle signs of menopause

In addition to inquiring about common menopausal symptoms, also ask about irritability, anxiety, sleeplessness, or agitation. Some women may not consider these symptoms to be menopausal or may be embarrassed to volunteer information about them.

Laboratory testing is usually not necessary to establish menopausal status

Clarifying whether or not a woman is perimenopausal or menopausal is usually a clinical diagnosis and laboratory testing is not required. Serum levels of follicle stimulating hormone (FSH) do not correlate with either intensity or frequency of hot flashes; it is fluctuation in estrogen levels that seems to be of greater significance.

For women with apparent menopausal symptoms who are younger than average (less than 40), or who continue to have apparently regular menses, testing may be useful; measure both FSH and estradiol (E2).

Testing may be most useful for the older woman (over age 50) on oral contraceptives (OCPs) who is interested in determining whether or not she can stop them. Measure FSH and estradiol as late as possible in the placebo week of pills.

Currently, there is insufficient evidence in the published scientific literature to permit conclusions concerning the use of salivary hormone testing for the diagnosis, treatment or monitoring of menopause and aging.

See Annotation Appendix E, Non-FDA-Approved Ht Treatment" in the original guideline document for more information.

Discuss current role of hormone therapy; address patient concerns

The widespread publicity surrounding the Women's Health Initiative (WHI) has left many providers and many patients with the impression that the published results preclude any clinical role for HT. Discuss these concerns with patients and help put recent studies in the proper context. There are many serious reservations about the methodology and the meaning of the results of the WHI trial. Also, because of the heterogeneity found in the estrogen and progesterone receptors in humans, all population studies are difficult to interpret to the individual.

Clarify that, by and large, any conclusions which may be drawn from the WHI and related studies apply primarily to the relatively long-term use of HT for disease prevention rather than its short-term use for menopausal symptom relief.

Although hormone therapy did protect against osteoporosis-related fractures, cardiac protection could not be demonstrated in the WHI. The trial was halted because the observed benefits could not be shown to be as great as originally expected and did not outweigh the observed risks.

Consequently, although widely recommended up until relatively recently, in current clinical practice HT is now seldom initiated solely for the prevention of chronic disease.

Hormone therapy remains the most effective treatment for the relief of hot flashes, as well as urogenital and other menopausal symptoms. However, for many women, other non-hormone options frequently provide adequate relief and should be considered.

In general, estrogen-only therapy (ET) may be less problematic than combination estrogen-progestin therapy (EPT), and transdermal estrogens (particularly in terms of the risk of venous thromboembolism) may not carry as much risk as oral estrogens. For a woman without a uterus, the short-term use of transdermal estrogen for menopausal symptom relief carries an extremely low risk. A more detailed discussion of these points follows throughout this guideline. (See Appendix C, "Provider Handout: HT Studies and Absolute and Relative Risks" in the original guideline document for an overview and risk table.)

Be aware that contraceptives, both pills (OCPs) and the transdermal patch, have much more potent estrogenic effects than HT, and that using or continuing OCPs or transdermal contraceptives in a perimenopausal woman cannot be considered in some way to be of less risk than initiating HT in the same woman.

A more detailed discussion of these points follows throughout this guideline. (See Appendix C, "Provider Handout: HT Studies and Absolute and Relative Risks" in the original guideline document for an overview and risk table.)

Ask about alternative therapies

A variety of herbal preparations and dietary supplements are marketed and used by patients as natural alternatives to HT. However, unless specifically asked, patients often do not volunteer information about their use.

These products may contain biologically active ingredients with significant physiologic effects. Their exact composition and consistency may be unknown or inconsistent. Very few products have been evaluated by well-controlled studies.

Patients will be well served and providers will gain credibility if factual information about alternative therapies is made available in a non-judgmental way. A strategy for guiding a discussion about the use, the known risks, and the potential benefits of several alternative therapies commonly used by menopausal women is included in Annotation Appendix E, "Non-FDA-Approved HT Treatments" in the original guideline document.

Counseling and education strategies

Women who actively participate in decision-making regarding their health care are more satisfied with their ultimate choices, especially if the approach

is tailored to the woman's individual situation and reflects her priorities and values. The long-term commitment to HT, for women who choose this option, is in turn strengthened in those women who are more satisfied with their decision.

Presenting information in a variety of formats, including written materials, books, videos, Internet sites, and discussion groups is most effective in supporting the collaborative decision-making process and in maintaining a woman's commitment to HT.

2a. Discuss Options for Menopausal Symptom Relief

Key Points:

- HT is the most effective treatment for hot flashes and other menopausal symptoms, although it is not always necessary and other options should be considered when appropriate.
- Not all sleep disorders among perimenopausal women are related to hormone changes; mood disorders or primary sleep disorders must also be considered.
- The association between hormone changes and the role of hormone therapy for memory and concentration, libido, mood, and many urinary symptoms is unclear.

Prior to menopause, often for several years, rising serum FSH levels and erratic ovarian follicle maturation lead to fluctuating and unpredictable estrogen and progesterone levels, accounting for many menopausal symptoms.

Most commonly, perimenopausal women experience menstrual irregularities, hot flashes, and vaginal dryness of varying degrees and severity. The sleep disruption from hot flashes may also lead to irritability, forgetfulness, and inability to concentrate. Fluctuating hormone levels are associated with emotional lability, but are not felt to be a direct cause of depression. Both disrupted sleep as well as urogenital changes can affect sexual functioning.

Hot Flashes and Night Sweats

Most women experience hot flashes (flushes) to some degree during the perimenopause. For many women, these symptoms are mild and of short duration, usually subsiding within five years, and do not require treatment beyond lifestyle adjustments, education, and reassurance.

For others, these symptoms may cause significant morbidity for many years and require additional treatment. Estrogen therapy is most effective, although various non-hormonal alternatives are sometimes helpful.

In particular, younger women who undergo oophorectomy will have a precipitous drop in estrogen levels, causing generally more severe and long-lasting hot flashes than women entering menopause spontaneously.

Characteristically, the hot flash involves an intermittent sensation of heat, flushing, and perspiration, usually limited to the head and upper torso. Some

women report a prodrome of head pressure. The flushing is sometimes reported to be associated with palpitations and episodes of feeling faint. Hot flashes occurring during the night are commonly called night sweats.

Lifestyle modifications: Exercise, lighter clothing, sleeping in a cooler room, and reducing stress may be sufficient to manage hot flashes for many women. Avoidance of possible triggers, including spicy foods, caffeine, smoking, and alcohol may help.

Hormone therapy: The most effective means of relieving hot flashes is hormone therapy.

Literature reviews indicate that hormone therapy will reduce the frequency of hot flashes by 80-90%. Therapy is usually limited to a few years, at most, and although the absolute risks are very low, they still must be fully discussed.

Selective estrogen receptor modulators (SERMs): SERMs are not indicated for menopausal symptom relief as they may actually worsen hot flashes.

Progestins: Megestrol and other progestins have been shown to reduce flushing. In patients with a history of breast or uterine cancer, megestrol decreased hot flashes by 80 percent.

Selective serotonin reuptake inhibitors (SSRIs): Venlafaxine (Effexor®), paroxetine (Paxil®), and fluoxetine (Prozac®) have been shown to be somewhat effective in relieving hot flashes. Perhaps two-thirds of women derive some benefit from these agents, compared to approximately one-third who may typically respond to placebo.

When effective, SSRIs in lower doses typically provide almost immediate relief from hot flashes, in distinction to the higher doses and much longer time frame needed to treat depression and other mood disorders. Consequently, a brief trial of a week or so may be sufficient to determine if an SSRI is going to be beneficial for hot flashes.

Other agents: There is some benefit for relief of hot flashes shown with other agents including gabapentin (Neurontin®), clonidine (Catapres®), methyldopa (Aldomet®), and belladonna-phenobarbital-ergotamine preparations (Bellergal® generics: Bellamine®] Bel-Pher-Ergot SR®), but various side effects limit their use.

See Appendix A, "Hormone Preparations" in the original guideline document for more information.

Phytoestrogens and isoflavones: Soy products or isoflavones, either through diet or supplementation, may not reduce the incidence of hot flashes. Inconsistencies among studies to date may be explained by different doses, products, sources, and processing. [Conclusion Grade III: See, Conclusion Grading Worksheet - Appendix A - Annotation #2a (Soy Products) in the original guideline document]

Herbal preparations and dietary supplements: Black cohosh, dong quai, evening primrose oil, flaxseed, ginseng, progesterone creams, red clover, and wild yam extract are commonly used but poorly studied. See Appendix E, "Herbal and Dietary Supplements" in the original guideline document for more information about these agents.

Vaginal Dryness

Urogenital tissues are highly estrogen-sensitive. Vaginal dryness and vulvovaginal irritation are increasingly common following menopause. Atrophy and lack of lubrication may cause dyspareunia.

Hormone therapy: While nonprescription vaginal lubricants and moisturizers may provide some relief (e.g., Astroglide or Replens), estrogens are far superior. Local treatment of these symptoms with estrogen (via intravaginal ring, tablet, or cream) is preferred. With the exception of the vaginal ring, there is little systemic absorption with commonly used dosages and minimal risk of side effects or endometrial hyperplasia. Vaginal estrogens significantly reduce the rate of recurrent urinary tract infections compared to placebo.

See Annotation Appendix A, "Hormone Preparations" in the original guideline document for specific guidelines for various vaginal estrogen preparations and delivery systems.

Sleep Disturbances

Not all sleep disorders among menopausal women are related to hormonal changes; mood disorders or primary sleep disorders must also be considered. Among menopausal-related sleep disturbances, night sweats are frequently the underlying cause, but some women may experience sleep disturbances without hot flashes.

Older women who discontinue HT after many years of use may develop new-onset sleep disturbances. These may be their only complaints and may not be recognized as being related to HT cessation.

Lifestyle modifications: Avoiding exercise late in the day, a hot shower or bath immediately prior to going to bed and maintaining regular bedtimes can help improve sleep. Over-the-counter sleep aids can also be helpful.

Hormone therapy: Estrogen will often relieve and improve sleep by the alleviation of night sweats. In addition, women frequently report an improvement in sleep patterns with HT even if hot flashes or night sweats are not prominent features of their menopausal symptoms.

Mood and Anxiety Disturbances

There is a complex interplay between fluctuating hormone levels and mood. The connection between mood lability and anxiety on the one hand, and other menopausal symptoms, especially disturbed sleep, on the other, is also

complicated. Social changes affecting menopausal women can also affect their mood and sense of well-being.

Women with a history of depression have a higher risk of menopausal mood disorders, but there is no direct association between menopause and depression. There is some evidence that estrogen may potentiate the effects of antidepressants, possibly by increasing or maintaining serotonin levels. Progestins may aggravate mood disturbances, perhaps negating any benefits of estrogen.

Lifestyle modifications: Adequate sleep, regular physical activity, and relaxation exercises may help with anxiety symptoms.

Hormone therapy: If there are other menopausal symptoms present, HT may be helpful. It is not known if estrogen has a direct effect on mood, irritability, or anxiety. These effects may be due solely to the alleviation of hot flashes and sleep disturbances.

Selective serotonin reuptake inhibitors (SSRIs): The SSRIs are most helpful if the underlying problem is a primary mood disorder or depression rather than a manifestation of hot flashes or disturbed sleep.

Concentration Difficulties and Forgetfulness

Menopausal women often report difficulties with concentration and short-term memory. These symptoms are more likely related to hot flashes and impaired sleep. Although biologically plausible, a direct association of these symptoms with female hormone level remains unproven.

There is little, if any, evidence of any relationship between these mild, subjective symptoms and the later development of dementia. These are separate clinical entities and it is important to make this distinction clear when counseling patients. (Current concepts regarding dementia and HT are discussed in Annotation #2c, "Discuss Limited Role of HT for Disease Prevention" in the original guideline document.)

Lifestyle modifications: Exercise and sleep hygiene appear to be just as helpful for improving subjective cognitive symptoms as other alternatives.

Hormone therapy: Cognitive symptoms may improve simply by alleviating hot flashes or sleep disturbances; if HT has any direct effect, it is relatively minor.

Decreased Libido and Sexual Dysfunction

Night sweats, mood lability, vaginal dryness, and sleep disturbances may significantly affect sexual function and libido. In addition, menopausal women confront significant social changes regarding their own sense of well-being and the sexuality of their partners. Discussing relevant internal and external social issues the patient is experiencing is worth consideration.

Hormone therapy: Besides relieving hot flashes and improving sleep, HT improves urogenital atrophy, thinning, dryness, and loss of elasticity, all which

may cause dyspareunia. While this will improve sexual functioning for many women, HT has no proven direct effect on sexuality or libido.

Paradoxically, there is evidence that oral estrogens, particularly conjugated equine estrogens (CEE), may decrease free testosterone (by elevating sex hormone globulins) which may further decrease libido.

Selective serotonin reuptake inhibitors (SSRIs): Treating an underlying depression or mood disorder may help sexual dysfunction, although the SSRIs frequently cause anorgasmia or other sexual side effects.

Androgen supplementation: Particularly after surgical menopause, androgen supplementation has been shown to increase libido. Standard doses have not been established and supraphysiologic doses, with potentially serious side effects, are often quoted in the literature. All women must have careful counseling before starting these agents.

Adding androgen to standard HT regimens may provide some additional value for the prevention and treatment of osteoporosis, but the exact benefit must await further studies. Any risk, however slight, may not be justified if there is no benefit of therapy.

Urinary Incontinence and Urgency

Urinary urgency and irritation, more frequent urinary tract infections, urinary incontinence, and pelvic support problems are also more common following menopause. However, the relationship between urinary incontinence and menopause is not well understood. Estrogen was long thought helpful in the treatment of incontinence, but newer evidence suggests that it may actually exacerbate the problem. Most studies have shown little improvement in urinary stress incontinence, although urge incontinence may be more responsive to HT.

Headache

Among many other causes, headaches may be associated with fluctuating estrogen levels in perimenopause.

Hormone therapy may stabilize hormone levels and alleviate headache symptoms. There are no contraindications to HT in women with migraines.

HT may occasionally cause or aggravate headaches; see Annotation #7, "Evaluate and Manage Side Effects" for guidelines for adjusting HT in these situations.

Other causes of headache and their treatment are discussed in the National Guideline Clearinghouse (NGC) summary of the Institute for Clinical Systems Improvement (ICSI) guideline Diagnosis and Treatment of Headache.

2b. Discuss Options for Long-Term HT Users; Ensure Continued Bone Health

Key Points:

- Women who have recently discontinued hormone therapy are at risk for rapid bone loss; they must be monitored appropriately to ensure continued bone health.
- If HT is still indicated, consider whether a lower dose or different formulation might be more appropriate

Women who have recently discontinued HT are at risk for rapid bone loss. They must be identified and monitored appropriately to ensure continued bone health.

Until recently, women who had been on HT without any problems rarely considered changing their regimens. With the publication of the WHI data and in the face of continued concern about HT, many women have discontinued it on their own; some have done well and others have experienced a recurrence of hot flashes and other symptoms. In addition, some women may be reluctant to volunteer this information unless specifically asked.

Some women want advice about strategies for stopping HT while minimizing symptoms, others wish reassurance about continuing HT, and still others want information about different formulations or regimens that may be safer in some way.

While the absolute risks of continuing HT are very low, they cannot be dismissed entirely and must be addressed.

While many different formulations and regimens for hormone therapy have been suggested and are being used by many practitioners, there is very little firm data to support these recommendations. However, there is some emerging data suggesting that transdermal estrogens may be less likely to increase the risk of venous thromboembolism (VTE) than oral estrogens, particularly CEE/medroxyprogesterone acetate (MPA).

Regularly evaluate each woman's need for hormone therapy.

- Consider the original indication for HT and whether it still remains.
- Check for the development of any medical conditions, particularly coronary heart disease (CHD), which might mandate greater caution.
- If HT is still indicated, consider whether a lower dose or different formulation might be more appropriate.

See Annotations 6b, "Guidelines for Modifying Hormone Therapy in Long-Term Users" and 6c, "Guidelines for Discontinuing Hormone Therapy in Long-Term Users" for guidelines for modifying hormone therapy regimens.

2c. Discuss Limited Role of HT for Disease Prevention

Key Points:

- Long-term hormone therapy is rarely initiated for the prevention of chronic disease.
- Recent data has called into question the long-held belief that HT protects against the development of CHD.

- HT protects against the development of osteoporosis and hip and vertebral fractures; several other agents are equally effective.

While HT has recently been proven to prevent osteoporotic fractures and lower the risk of colon cancer, current practice largely limits its role to the treatment of menopausal symptoms.

HT is seldom initiated solely for long-term disease prevention. However, in light of the uncertainty about the role of HT, current concepts regarding its relationship to several chronic conditions are summarized below.

Osteoporosis: Prevention of osteoporosis has been the most well-documented and widely accepted use of HT. While observational studies had indicated that HT provided protection against hip and vertebral fractures, the Women's Health Initiative (WHI) was the first randomized trial to confirm this finding.

See the NGC summary of the ICSI guideline Diagnosis and Treatment of Osteoporosis for specific recommendations regarding bone mineral density (BMD) testing and osteoporosis treatment.

The benefits of HT are maintained as long as it is continued, but bone loss resumes when treatment is stopped, and any residual benefit is rapidly lost. Bone mineral density should be measured when women discontinue HT after several years of use.

Several other agents are as effective as hormone therapy in preventing fracture due to osteoporosis; these include:

Bisphosphonates: Alendronate (Fosamax®), risedronate (Actonel®, and ibandronate (Boniva®) are commonly used for both prevention and treatment of osteoporosis. Their use may be complicated by esophageal irritation, but proper dosing minimizes this problem. Bisphosphonates in combination with estrogen are more effective than either agent alone.

Selective estrogen receptor modulators (SERMs): SERMs (e.g., raloxifene [Evista®] are indicated for the prevention and treatment of osteoporosis. They are not indicated for the treatment of menopausal symptoms and may even aggravate hot flashes in some women. They also do not help vaginal atrophy. As with estrogen, a past history of venous thrombosis is a contraindication to their use. Current venous thrombosis is an absolute contraindication.

Calcitonin (Miacalcin®): A nasal spray used for osteoporosis treatment that inhibits bone resorption and reduces fracture rates. Nasal irritation and cost limit its use.

Parathyroid hormone (PTH e.g., teriparatide [Forteo®]): Daily subcutaneous injections are used for osteoporosis treatment. PTH is Food and Drug Administration (FDA) approved but carries a black box warning about possible risk for osteosarcoma based on rat studies.

Refer to the NGC summary of the ICSI guideline Diagnosis and Treatment of Osteoporosis for specific recommendations.

Coronary heart disease (CHD): Recent data has called into question the long-held belief that HT protects against the development and progression of CHD.

Many observational studies and known biologic effects suggested a beneficial effect of estrogen for CHD prevention. However, more recent prospective randomized controlled trials (WHI, others) have not shown any benefit of HT for either primary or secondary prevention, and have suggested that HT may even cause myocardial infarction.

These discrepancies continue to be hotly debated. The observational studies may have been affected by selection bias, in that healthier women with better access to health care are more likely to use HT. Alternatively, the prospective trials may have been confounded by the inclusion of older women with preexisting CHD. There are also experimental data from nonhuman primates which could explain these discrepancies. Further randomized trials in women as they enter menopause, comparing transdermal to oral estrogen, such as the Kronos Estrogen, Estrogen/Progesterone (KEEPS) trial may also help explain these paradoxes. While estrogen given in early menopause may prevent atherosclerosis, later estrogen use, after lesions develop, may actually precipitate coronary events.

Progestins may also account for the deleterious effects of HT. However, there is no specific evidence that estrogen alone is safer or more beneficial.

Specific recommendations from several sources currently include the following:

- Identify and treat all CHD risk factors.
- Do not initiate HT for the prevention of CHD.
- Do not initiate HT in patients with known CHD.
- If CHD develops while on HT, consider other alternatives.

Alzheimer's disease (AD): Some studies have indicated that HT may improve cognitive functioning in perimenopausal women, but this may be due solely to the alleviation of menopausal symptoms. It is unknown whether long-term HT has any benefit for the prevention or progression of dementia, including AD. More recent studies have reported an increased risk of dementia among older women taking HT.

Again, these discrepancies may be explained by selection bias, by the inclusion of older women who were past a "window" in early menopause when HT would have been helpful, or by other factors. Additionally, there are studies on the cellular level that demonstrate neuroprotective effects of estrogen. These findings have significance in that there are demonstrated improvements in balance and reflexes in estrogen users. As with the controversy surrounding CHD, the exact relationship between AD and HT is uncertain and may remain so for quite some time.

Colorectal cancer: The WHI estrogen-progestin (EPT) arm confirmed that HT lowers the risk of developing colon cancer. The estrogen-only arm did not show a reduction in colon cancer. However, HT should not be used solely for colon cancer prevention and women taking HT still need colorectal cancer screening at the recommended intervals.

Skin/Wound healing: HT has beneficial effects on collagen metabolism, improving skin tone and wound healing, but it should not be initiated solely for that purpose.

Tooth loss: HT reduces maxillary and mandibular osteoporosis and prevents resulting tooth loss, but it should not be initiated solely for that purpose.

Macular degeneration: HT reduces the risk of developing age-related macular degeneration, but it should not be initiated solely for that purpose.

3. Discuss HT Risks and Contraindications

Key Points:

- There may be a small increase in breast cancer risk after several years of HT, although this continues to be debated.
- Progestins added to the HT regimen largely eliminate any increased risk of endometrial cancer.
- The risk for venous thromboembolism (VTE) is increased approximately twofold in current, but not former, users of HT, although the absolute risk is still very low.

Breast cancer: The possible increased risk of breast cancer with HT is a primary concern of many women. Many investigators, including those associated with the WHI, have indeed reported a relationship between HT and the development of breast cancer. Others view any apparent increase as statistically insignificant or even spurious.

There may be a small increase in breast cancer risk after several years of hormone therapy. Women who take HT for less than 3 years (e.g., for menopausal symptom relief) may not be at any increased risk. If real, the absolute risk after 3 to 5 years is small, on the order of approximately one additional breast cancer per 1,000 women per year. Recent studies also suggest that any increased risk may be related to the progestin in combined EPT, rather than the estrogen itself.

Earlier studies seemed to indicate that breast cancer mortality did not seem to be increased with hormone therapy, and the breast cancers arising in women on HT tended to be less advanced and to have more favorable prognoses. More recent studies have reported a trend toward increased tumor size, lymph node involvement, and stage at time of diagnosis, in HT users. These studies also demonstrated an increased frequency of abnormal mammograms among HT users.

In summary, more prolonged use of HT may increase the risk of developing breast cancer, or it may simply stimulate the growth of preexisting breast cancers, or there may be other explanations for the observed data. Whatever the case, this possible increased risk cannot be dismissed and the limitations of current knowledge must be discussed. As with other potential risks of HT, there is no evidence that different formulations or lower doses of estrogens are necessarily of any lesser risk than those more widely used or studied.

Endometrial cancer: The risk of developing endometrial cancer is increased only in women taking unopposed estrogen. Any additional risk is largely eliminated when progestogen is added to the HT regimen.

Unopposed estrogen results in a significant increase in the risk of endometrial hyperplasia after only one to three years. Endometrial hyperplasia may eventually lead to atypical hyperplasia and even malignancy if unopposed estrogen is continued.

Gallbladder disease: Observational studies, as well as more recent prospective trials, suggest that the risk of gallbladder disease (cholelithiasis, cholecystitis) and cholecystectomy is increased in women taking HT. This effect was seen in women taking estrogen only as well as estrogen/progestin combination therapy.

Venous thromboembolism (VTE): The risk for VTE appears to be increased approximately twofold in current, but not former users of HT. The absolute risk is still relatively low, being increased from approximately 15 cases per 10,000 women in the general population to approximately 30 cases per 10,000 women on HT. Transdermal estrogens do not seem to carry the increased risk of VTE seen with oral estrogens. In experimental studies, the deleterious effects of oral estrogens on several different clotting parameters, including APC sensitivity, protein C, and fibrinolysis, were not seen with transdermal estrogens.

Be aware that transdermal contraceptives have much more potent estrogenic effects than the transdermal formulations used for hormone therapy and cannot be similarly considered to be of less risk than oral estrogens.

Myocardial infarction: There does not appear to be an overall effect on the rate of fatal myocardial infarction associated with an HT regimen, although the EPT arm of the WHI trial noted an increase in the rate of nonfatal MI. The estrogen-only arm did not show an increase in myocardial infarction.

Alzheimer's disease: There are discrepancies in the evidence that estrogen has any specific effects on cognitive performance. The Women's Health Initiative Memory Study (WHIMS) indicated that hormone therapy adversely affects global cognition, which includes memory and other basic mental abilities including concentration, language, and abstract reasoning. In particular, EPT doubled the risk of dementia in older women. In the ET group, there was a weaker, but similar trend in the results.

Ovarian cancer: There may be a weak association between the prolonged use of estrogen and ovarian cancer, but no epidemiological evidence has been established.

Contraindications to HT:

Unexplained vaginal bleeding and pregnancy: These are temporary but absolute contraindications to HT.

Past history of breast cancer or endometrial cancer: While usually considered contraindications to HT, short-term use for severe menopausal symptoms may be considered with proper precautions.

An increasing number of younger women are being cured of breast cancer, and some of these women may require treatment for severe vasomotor symptoms or significant vaginal atrophy. Short-term oral or transdermal HT or intravaginal estrogen may be considered after consultation with an oncologist.

Most oncologists agree that women with past history of stage I endometrial cancer which has been successfully treated may safely use HT if it is otherwise indicated.

Women with a past history of venous thrombosis are at increased risk for recurrence; however, taking oral contraceptives (OCPs) or HT confers an overall low increase to this risk of recurrence.

Family history of premenopausal breast cancer: In the Iowa Women's Health Study there was not an increased incidence of breast cancer in HT users with a family history of breast cancer, relative to those HT users without a family history of cancer.

Hypertriglyceridemia: Oral estrogens are contraindicated because of the danger of precipitating pancreatitis. Transdermal estrogens or intravaginal estrogens, which avoid the first-pass hepatic effect, do not carry this risk.

Chronic liver disease: Oral HT is a relative contraindication. Again, transdermal and intravaginal estrogen avoids the first-pass hepatic effect of oral HT.

HT is not contraindicated in these clinical settings where many practitioners have often been reluctant (often unjustifiably so) to recommend oral contraceptives; OCPs have much more potent estrogenic effects than HT. These conditions include:

- endometriosis
- fibrocystic breast disease
- hypertension
- mastalgia
- migraine headaches
- obesity

- tobacco use
- uterine leiomyomata (fibroids)

4. Collaborative Decision-Making: Clarify Patient's Values and Priorities

   Key Points:

   - Careful consideration and in-depth discussion are required whenever the initiation or continuation of hormone therapy is considered.
   - Address the discrepancies and gaps in our knowledge and address any factual misunderstandings.
   - Help each woman clarify her individual values and priorities so that she may decide how important each of the potential benefits and risks of HT is to her unique situation.

   Truly collaborative decision-making requires that each woman clarify her individual values and priorities, with help from her provider if she wishes, so that she may decide how important each of the potential benefits and risks of HT is to her unique situation.

   Inquire about each woman's particular goals and concerns about menopause and her attitudes toward taking medications in general and hormone therapy in particular.

   Clarify the distinction between long-term HT for preventive therapy and its short-term use for symptom relief.

   Discrepancies among the various studies continue to be debated, and it is unlikely that definitive information or consensus will be available anytime soon. Acknowledge this uncertainty and take the necessary time for an in-depth discussion with women who are considering either starting or continuing hormone therapy. It is often helpful to discuss the patient's understanding and perception of the risks of HT and of various conditions and to help put them in perspective.

   Many women consider any possible increased risk of breast cancer to outweigh any possible benefit of HT.

   Many women find the prospect of the resumption or continuation of their menses to be unacceptable, or consider irregular spotting to be too worrisome to justify HT use.

   Some women consider any use of HT to represent the unnecessary medicalization of menopause. Others may value alternative therapies for menopausal symptoms more highly than traditional medical practices. Some women object to conjugated equine estrogens because of animal cruelty concerns.

   Misunderstandings about hormone therapy are not infrequent; help women address these and other concerns.

- Many women believe that they must always take estrogen if they once start, or that their menses will continue indefinitely on HT
- Many women believe that use of hormone therapy merely postpones the occurrence of menopausal symptoms to a later date
- Many women overestimate their baseline risk of breast cancer

Individual women, even if they have identical clinical situations, will often arrive at completely different decisions regarding hormone therapy. As long as the decision is right for each individual patient, it is the appropriate choice.

There is no best or easy approach to this step of the decision-making process. Patience, insight, and care are required to recognize different perspectives and to achieve a respectful and balanced discussion about HT and midlife women's health.

6a. Guidelines for Initiating Hormone Therapy

Key Points:

- There is no firm evidence that any one form of estrogen or progestin is superior to another, although different preparations are useful in different clinical settings.
- Progestins are not necessary in women who have had a hysterectomy.

Jointly decide on the hormone therapy regimen best suited to each woman's particular characteristics and needs.

There is no firm evidence that any one form of estrogen or progestin is superior to another. On the other hand, transdermal estrogens do not show the same deleterious effects on clotting parameters as oral estrogens.

Estrogen-Progestin (EPT-Combined) vs. Estrogen-Only (ET) Hormone Therapy

Progestins are combined with estrogen to prevent endometrial hyperplasia and to minimize the risk of endometrial cancer in women with an intact uterus.

Progestins are not necessary in women who have had a hysterectomy.

Progestins are also not necessary in women receiving intravaginal estrogens; the systemic absorption is insufficient to cause endometrial hyperplasia even if they have an intact uterus.

Please refer to Appendix A, Table IV "Combination Estrogen-Progestin Preparations" in the original guideline document for information on delivery mode and dosage.

Cyclic vs. Continuous Combined Hormone Therapy

The terms cyclic and continuous refer only to the progestogen component of combined HT.

Oral estrogen should always be given every day; there is no advantage to the once popular intermittent dosing as it may cause increased hot flashes or migraines during the time that estrogen is withheld.

Progestins may be given either cyclically (generally in the earlier years of perimenopause) or continuously (generally later in menopause) as detailed below.

European evidence suggests that continuous progestin/estrogen use may reduce by 80% the risk of endometrial cancer compared with five or more years of cyclic estrogen/progesterone which showed a 60% increase in risk of endometrial cancer over no treatment. Because different HT agents are used in Europe, the applicability of this finding to U.S. medical practice has been questioned.

For information on delivery mode and dosage of combination estrogen-progestin preparations, estrogen preparations and progesterone/progestin preparations, see Annotation Appendix A, "Hormone Preparations," in the original guideline document.

Discuss Expected Bleeding Patterns

Younger women with occasional menses may still be having intermittent ovarian activity. Initiating HT with a cyclic progestin regimen minimizes irregular bleeding and spotting and usually results in a predictable monthly withdrawal bleed. Some women may achieve eventual amenorrhea, although it may require several months or longer.

Older women who have been on cyclic therapy for two to three years may be switched to continuous combined HT. If they have been amenorrheic on cyclic HT, they are likely to remain so on combination HT. However, even if they have been having light withdrawal bleeding, they may still become amenorrheic on combined HT.

Theoretically, menopausal women who have been amenorrheic for some time could be started directly on combination therapy, but as a practical matter, HT is rarely initiated in these women.

Continuous oral progestin may cause unpredictable vaginal bleeding, with or without spotting, for many months. Five to 20% of these women may never achieve amenorrhea and may opt for cyclic hormone therapy to achieve a more predictable bleeding pattern.

Discuss Possible Side Effects

Estrogenic side effects: Mastalgia, fluid retention, nausea, leg cramps, and aggravation of headaches are all side effects to estrogen therapy. Rarely, estrogen may cause an unexpected rise in blood pressure.

Reassure women with mastalgia that it is not in any way associated with an increased risk of breast cancer.

Progestin side effects: Fluid retention and bloating, headache, mastalgia, oily skin and acne, mood alterations, and premenstrual-type symptoms are possible side effects.

Although studies using progestins versus progesterone in HT have shown similar side effect profiles, some patients may have fewer side effects or less severe side effects with progesterone preparations.

Refer to Annotation #7, "Evaluate and Manage Side Effects," for further details and specific management guidelines.

Prescribing hormone therapy: There is no firm evidence that any particular form or dose of oral estrogen or progestin is superior to another. On the other hand, transdermal estrogens do not carry the same increased risk of VTE seen with oral estrogens.

Although there is not evidence from randomized, controlled trials, several authorities make the reasonable recommendation to use the lowest possible dose for the shortest possible time (e.g. American College of Obstetricians and Gynecologists [ACOG], NIHMS, and National Institute of Health [NIH]).

Hormone therapy for hot flashes: Doses as low as 0.025 milligrams (mg) of transdermal estradiol, 0.5 mg of oral estradiol, or 0.3 mg of CEE may be effective.

Following surgical menopause, some women may require as much as 2.5 mg CEE or 2 mg estradiol daily for effective symptom relief.

Hormone therapy for urogenital symptoms: If needed for urogenital symptoms only, consider intravaginal estrogens in the form of cream, gel, or ring.

Systemic estrogens (either oral or transdermal) may be required to have an effect on urinary epithelium for alleviation of frequency, urgency, or incontinence.

Women Who May Still Need Contraception

Younger perimenopausal women with irregular menses and hot flashes may still be occasionally ovulating. Consider low-dose OCPs rather than HT to control symptoms, and minimize irregular bleeding while providing still-needed contraception. OCPs are contraindicated in women age 40 who smoke. Prescribe low-estrogen OCPs to minimize any risk of thromboembolic events.

Be aware that contraceptives, both pills (OCPs) and the transdermal patch, have much more potent estrogenic effects than HT, and that using or continuing OCPs or transdermal contraceptives in a perimenopausal woman cannot be considered in some way to be of less risk than initiating HT in the same woman.

Laboratory testing may be helpful for the older perimenopausal woman (over age 50) on OCPs who is interested in determining whether or not she can stop her birth control medication. Measure follicle stimulating hormone (FSH) and estradiol (E2) as late as possible in the placebo week of pills.

6b. Guidelines for Modifying Hormone Therapy in Long-Term Users

Key Points:

- Many women may require continued HT for adequate menopausal symptom relief, although older women may be able to decrease their dose without precipitating the resumption of hot flashes.
- While not proven, it seems prudent to use transdermal estrogen, in the lowest effective dose, when possible
- There is very little evidence supporting the use of unopposed estrogen (as a strategy to eliminate possible progestin-related risks), even with careful endometrial surveillance. However, for individual women, this may be the only effective alternative for intolerable hot flashes.

Many women may require continued hormone therapy for adequate menopausal symptom relief; they must be fully informed of the risks and benefits and have regular follow up.

There is very limited data to suggest that different formulations or dosing regimens are significantly safer than those which have been better studied or more widely used (conjugated equine estrogens [CEE]/medroxyprogesterone acetate [MPA]). Nonetheless, it seems prudent to use transdermal estrogen, in the lowest effective dose, when possible. Many older women may be able to decrease their dose of estrogen without precipitating the resumption of hot flashes.

There is good evidence that lower doses of estrogen (CEE 0.3 mg daily, estradiol 0.5 mg daily, 0.025-0.05 mg transdermal estradiol) maintain bone density nearly as well as higher doses. Continue to monitor bone density in the first year after decreasing the estrogen dose.

Transdermal estrogen has a better side effect profile and an apparently lower risk of VTE than oral estrogens.

Although progestins may be responsible for an increased breast cancer risk in long-term users of combination EPT, there is little, if any, evidence to support using "long cycle" progestin dosing (12 to 14 days of progestin every 3 to 6 months) or the progestin secreting intrauterine device (IUD) as a risk reducing strategy. Furthermore, there is no evidence at all to support using of unopposed estrogen, even in low doses and with careful endometrial surveillance, for this purpose. (These may, however, be among the only reasonable alternatives for women who cannot tolerate progestins and have intolerable hot flashes that are not relieved by non-hormonal medications. See Annotation #7, "Evaluate and Manage Side Effects," for further information.)

6c. Guidelines for Discontinuing Hormone Therapy in Long-Term Users

Key Points:

- There is very little firm data to support these recommendations or guide practitioners for discontinuing hormone therapy in long-term users.

- Women may undergo rapid bone loss upon stopping; bone health, specifically bone density, must be considered and carefully monitored.

Many regimens have been suggested and are being used by many practitioners for discontinuing hormone therapy in long-term users, but there is very little firm data to support these recommendations or guide this process.

Many women do not notice any symptoms even with abrupt cessation of HT, while others may experience a recurrence of hot flashes. In older menopausal women, sleep disorders, rather than hot flashes, may be the major manifestation of renewed menopausal symptoms.

There is some biologic basis for recommending tapering hormone therapy over several months rather than stopping abruptly. As the washout period of CEE is longer than with other forms of estrogen, switching to a different formulation, such as estradiol, may also be helpful.

Consider alternative therapies for menopausal symptom relief, as outlined in Section 2a, while tapering HT.

As noted before, no matter how long a woman has been on HT, she may undergo rapid bone loss upon stopping. Bone health, specifically bone density, must be considered and carefully monitored.

7. Evaluate and Manage Side Effects

   Key Points:

   - Irregular bleeding usually resolves within 6 to 12 months following initiation of HT; try to avoid changing regimens too quickly.
   - Bleeding occurring after 12 months of amenorrhea should be considered as an episode of postmenopausal bleeding and appropriately evaluated.
   - Any bleeding pattern which is of concern, based on the clinical judgment of the provider, should be appropriately evaluated.

   The decision to take HT is often reached after considerable soul-searching by the patient. Her continued use of HT will likely be further dependent on the nature and resolution of any significant side effects that occur.

   Bleeding

   Irregular bleeding following the initiation of HT is very common. Advising the patient of this before initiating therapy may strengthen adherence. See "Discuss Expected Bleeding Patterns" in Annotation #6a, "Guidelines for Initiating HT" for a summary of expected patterns of continued or irregular bleeding.

   For most women, irregular bleeding improves within approximately 6 to 12 months of initiating HT; changing HT regimens or formulations too quickly is unlikely to be helpful.

Evaluation of "abnormal" bleeding

There are no universally accepted criteria for defining "abnormal" bleeding and mandating further evaluation. Most bleeding is due to benign cause; early stage endometrial cancer is virtually always curable, so it is important to detect early.

The guideline developers believe the following criteria are reasonably cautious but minimize unnecessary endometrial biopsies.

For women on cyclic HT: Cyclic withdrawal bleeding is to be expected. Evaluate any unusually prolonged or heavy bleeding occurring near the end of the progestogen phase of the cycle, or breakthrough bleeding occurring at any other time.

For women on continuous HT: Irregular bleeding may often persist for six to 12 months; evaluate any bleeding that persists any longer than this or that occurs after amenorrhea has become established.

Methods of endometrial assessment

There are various modalities used to evaluate abnormal bleeding, including endometrial sampling (biopsy or dilation and curettage [D & C]), endovaginal ultrasound (EVUS), sonohysterography, and hysteroscopy.

Given the strengths and limitations of both EVUS and endometrial biopsy, many experts advocate combining the two tests. Other tests, such as D&C, hysteroscopy, and saline intrauterine infusion during EVUS, are better reserved for cases where EVUS and endometrial biopsy results are equivocal.

Finally, in the asymptomatic HT patient found to have a thickened endometrium by EVUS evaluation and subsequent negative findings at endometrial biopsy, at least one study shows additional sampling is not warranted.

Endometrial sampling (biopsy and D&C): The historical "gold standard" for histologic evaluation of the endometrium has been dilation and curettage (D&C), yet this surgical procedure has a known false negative rate of 2 to 6%. Furthermore, D&C requires an operating room setting with attendant risks of anesthesia, hemorrhage, infection, and uterine perforation. Finally, cost considerations make the procedure impractical for first-line evaluation of endometrial thickness.

In response to this problem, several collection devices to allow for endometrial sampling (endometrial biopsy) in an outpatient setting have been created. However, these devices have a greater false negative percentage than D&C, and can be successfully employed in only about 70-80% of postmenopausal women.

Endovaginal Ultrasound (EVUS): Endovaginal ultrasonographic (EVUS), alone or in conjunction with endometrial sampling, has been advocated as a

safe and cost-effective method for evaluating a patient on HT for endometrial hyperplasia.

A positive correlation between an increase in endometrial thickness detected on EVUS and endometrial pathology, ranging from endometrial polyps to endometrial hyperplasia to endometrial carcinoma, has been demonstrated.

Sonohysterography: Sonohysterography is performed by instilling 10 cc of sterile saline into the uterine cavity via a flexible catheter. This technique separates the two walls of the endometrium and produces a sonolucent window through which endometrial thickness can be completely examined.

Sonohysterography can detect focal areas of endometrial thickening, which suggests a true pathologic condition is present. In particular, sonohysterography is useful in delineating polyps and submucous fibroids. Endometrial sampling via directed endometrial biopsy, dilatation and curettage, or operative hysteroscopy is needed to complete the evaluation under these circumstances.

Hysteroscopy: Hysteroscopy involves the use of a fiberoptic viewing scope and a distending medium to directly view the endometrial cavity. There are a wide variety of such devices and media. Some hysteroscopes have been designed for use in an office setting with minimal or no anesthesia or sedation, using carbon dioxide as a distending medium.

The ability to directly visualize potentially pathologic tissue has led many in the field to now define hysteroscopy as the "gold standard." However, major disadvantages to this procedure include the cost, operator learning curve, and the difficulty to use hysteroscopy in the face of cervical stenosis or active uterine bleeding.

Management of bleeding occurring while on cyclic HT

Most often, irregular bleeding occurring after the initiation of cyclic HT will resolve within a few months, when ovarian function ceases completely.

If intervention becomes necessary, increase the progestogen dose, if tolerated. If endometrial biopsy is performed, persistent proliferative activity during the progestogen phase gives further weight to this approach.

If HT is initiated in a woman who has been amenorrheic for many years, continuous therapy is preferred as cyclic HT may lead to a resumption of menses/bleeding.

Management of bleeding occurring while on continuous HT

Some women may have irregular spotting and bleeding for many months after initiating continuous HT. Many of these women may end up switching back to cyclic, so that their bleeding patterns are at least predictable.

Persistent bleeding while on continuous HT is usually due to an unstable atrophic endometrium. It may resolve with an increased progestogen dose or with the use of a levonorgestrel-secreting IUD.

Weight Gain

Around menopause, most women gain weight and experience an increase in their proportion of central abdominal fat. Contrary to various widely-held beliefs, this is neither caused nor alleviated by hormone therapy.

Some women experience breast tenderness and fluid retention shortly after initiating HT and these symptoms may contribute to a subjective sense of weight gain; they will usually resolve after a few months.

Patient education that anticipates concerns about weight gain may be helpful. Weighing patients at each visit may help reassure them that although their body fat distribution may change, actual weight over time is relatively stable.

Management of Headache

As discussed in more detail in Annotation #2a, "Discuss Options for Menopausal Symptom Relief," estrogen therapy may occasionally aggravate migraine headaches. Switching to a lower dose or from oral to transdermal estrogen (with more even absorption) may be helpful.

Management of Estrogenic Side Effects

Common estrogenic side effects are listed in Annotation #6a, "Guidelines for Initiating HT."

Fluid retention and headache may be related to either estrogen or progestins; modifying the progestogen first is usually the better strategy (see below).

Breast tenderness is more likely to be alleviated with lower estrogen dosages, although adjusting the progestogen may occasionally be effective if the symptoms seem to have a cyclic quality (see below).

Switching to the transdermal estrogen preparations may alleviate nausea.

Management of Progestogenic Side Effects

Common progestogenic side effects are listed in Annotation #6a, "Guidelines for Initiating HT."

Fluid retention and headache are most likely related to progestins. However, if a different formulation of progestogen is not helpful, consider modifying the estrogen component (see above).

Although MPA has been among the most widely used progestins, other agents, especially micronized progesterone (Prometrium) may be better tolerated.

Continuous HT, with more constant systemic absorption than cyclic HT, may be tried for the relief of mastalgia, headaches, and premenstrual-type symptoms if adjusting the two components individually is not effective.

The levonorgestrel-secreting IUD and vaginal progesterone suppositories keep systemic absorption to an absolute minimum and provide adequate endometrial protection for women on low-dose estrogen.

Using cyclic progestogens for a full 12 to 14 days but only every 3 to 6 months also minimizes side effects. This regimen may also provide adequate endometrial protection, but the studies are small and the data is limited.

Ultimately, for a few women who cannot tolerate progestins at all, unopposed low-dose estrogen may be the only reasonable alternative for severe hot flashes unrelieved by non-hormonal medications. In this situation, informed consent, careful clinical judgment, and regular endometrial surveillance are essential.

8. Follow-Up/See Related ICSI Guidelines

Key Points:

- Provide support and encouragement, through accessibility and close follow-up, for women who have recently initiated hormone therapy.
- Regularly evaluate each woman's ongoing need for hormone therapy.
- Be aware of changes in understanding and in standards of care associated with hormone therapy.

Up to one-third of women will need to modify or change their hormone therapy regimen if they are to be successful in its use. Consequently, follow-up and stay in contact within the first few months after initiating hormonal therapy. Research has shown that a significant number of patients never even fill their prescriptions or discontinue hormone therapy, often without their provider's knowledge.

For women on a stable HT regimen, reassess their need for continuing therapy on a regular basis:

- Consider the original indication for HT and whether it is still valid.
- Check for the development of any medical conditions, particularly CHD, which might mandate greater caution.
- Consider whether a lower dose or different formulation might be more appropriate.

For women who may have stopped HT since their last encounter, consider bone mineral density measurement. (See also Annotation #6c, "Guidelines for Discontinuing HT in Long-term Users," for additional information on this topic.)

The knowledge and understanding of the role of hormone therapy, as well as the standards of care associated with its use, are frequently changing. The

provider should be aware of any new clinical studies or practice guidelines that become available, in order to best serve the needs of patients.

Definitions:

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Nonrandomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

CLINICAL ALGORITHM(S)

A detailed and annotated clinical algorithm is provided for Menopause and Hormone Therapy (HT): Collaborative Decision-Making and Management.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is classified for selected recommendations (see "Major Recommendations" field).

In addition, key conclusions contained in the Work Group's algorithm are supported by a grading worksheet that summarizes the important studies pertaining to the conclusion. The type and quality of the evidence supporting these key recommendations (i.e., choice among alternative therapeutic approaches) is graded for each study.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Increased percentage of perimenopausal/menopausal women who receive education describing risk and benefits of hormone therapy (HT)
- Increased percentage of women with appropriate follow-up to cessation of HT

POTENTIAL HARMS

Refer to the "Major Recommendations" field for detailed discussion of the possible risks and side effects associated with Hormone Therapy.

CONTRAINDICATIONS

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Absolute Contraindications to Hormone Therapy

- Unexplained vaginal bleeding and pregnancy are temporary but absolute contraindications to hormone therapy (HT).
- Past history of breast cancer or endometrial cancer is usually considered a contraindication to HT; short-term use for severe menopausal symptoms may be considered with proper precautions.
- Women with a past history of venous thrombosis are at increased risk for recurrence; however, taking oral contraceptives (OCPs) or HT confers an overall low increase to this risk of recurrence.
- Hypertriglyceridemia is a contraindication to oral estrogens because of the danger of precipitating pancreatitis. Transdermal estrogens or intravaginal estrogens, which avoid the first-pass hepatic effect, do not carry this risk.

Relative Contraindications

Chronic liver disease is a relative contraindication to oral HT. Transdermal and intravaginal estrogen avoid the first-pass hepatic effect of oral HT.

Other Contraindications

- Oral contraceptive pills (OCPs) are contraindicated in women over age 40 who smoke.
- Chaste tree berry is contraindicated with OCP and other hormone therapies. Its safety during pregnancy and lactation is controversial.
- Red clover is contraindicated with OCP, anticoagulants, in pregnancy and lactation, and estrogen-dependent cancers.
- A past history of venous thrombosis is a contraindication to use of selective estrogen receptor modulators (SERMs). Current venous thrombosis is an absolute contraindication.

QUALIFYING STATEMENTS

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- These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.

- This guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situations and any specific medical questions.
- With the early termination of one arm of the Women's Health Initiative (WHI) trial in July 2002, and the attendant media coverage, apprehension about hormone therapy has steadily increased. Discrepancies among the various studies continue to be debated, and it is unlikely that definitive information or consensus will be available anytime soon. The fact remains that neither the known or postulated benefits of long-term hormone therapy (HT) for prevention can be proven to outweigh the potential risks associated with its use. On the other hand, there is no rational basis for the extreme view that HT is of such high or unique risk that it has no role in clinical care, particularly for menopausal symptom relief. Given this uncertainty, careful consideration and more in-depth discussion are required whenever the initiation or continuation of hormone therapy is considered. Women should be fully informed of the strongest available evidence regarding the benefits and risks of HT. The health status of every woman should be thoroughly evaluated so that informed decisions about HT use can be made. Truly collaborative decision-making requires that each woman clarify her individual values and priorities, with help from her provider if she wishes, so that she may decide how important each of the potential benefits and risks of HT is to her unique situation.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for release, a member group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

Detailed measurement strategies are presented in the original guideline document to help close the gap between clinical practice and the guideline recommendations. Summaries of the measures are provided in the National Quality Measures Clearinghouse (NQMC).

IMPLEMENTATION TOOLS

Clinical Algorithm
Patient Resources
Pocket Guide/Reference Cards
Quality Measures

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

RELATED NQMC MEASURES

- Menopause and hormone therapy (HT): collaborative decision-making and management: the percentage of women in menopause who have had a bone mineral density (BMD) measurement after cessation of HT.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Menopause and hormone therapy (HT): collaborative decision-making and management. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2005 Aug. 64 p. [176 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Aug (revised 2005 Aug)

GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

Organizations participating in the Institute for Clinical Systems Improvement (ICSI): Affiliated Community Medical Centers, Allina Medical Clinic, Altru Health System, Aspen Medical Group, Avera Health, CentraCare, Columbia Park Medical Group, Community-University Health Care Center, Dakota Clinic, ENT Specialty Care, Fairview Health Services, Family HealthServices Minnesota, Family Practice Medical Center, Gateway Family Health Clinic, Gillette Children's Specialty Healthcare, Grand Itasca Clinic and Hospital, HealthEast Care System, HealthPartners Central Minnesota Clinics, HealthPartners Medical Group and Clinics, Hutchinson Area Health Care, Hutchinson Medical Center, Lakeview Clinic, Mayo Clinic, Mercy Hospital and Health Care Center, MeritCare, Mille Lacs Health System, Minnesota Gastroenterology, Montevideo Clinic, North Clinic, North Memorial Care System, North Suburban Family Physicians, Northwest Family Physicians, Olmsted Medical Center, Park Nicollet Health Services, Pilot City Health Center, Quello Clinic, Ridgeview Medical Center, River Falls Medical Clinic, Saint Mary's/Duluth Clinic Health System, St. Paul Heart Clinic, Sioux Valley Hospitals and Health System, Southside Community Health Services, Stillwater Medical Group, SuperiorHealth Medical Group, University of Minnesota Physicians, Winona Clinic, Ltd., Winona Health

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GUIDELINE COMMITTEE

Ob/Gyn Steering Committee

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

In the interest of full disclosure, the Institute for Clinical Systems Improvement (ICSI) has adopted a policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. The reader should not assume that these financial interests will have an adverse impact on the content of the guideline. Readers of the guideline may assume that only work group members listed below have potential conflict of interest to disclose.

June LaValleur, MD has been a member of the speakers bureau for Ciba-Geigy, Merck, Parke-Davis, Solvay, Wyeth Ayerst, Eli Lilly, Health Learning Systems, Pharmacia, Procter & Gamble, and Pfizer.

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No other work group members have potential conflicts of interest to disclose.

ICSI's conflict of interest policy and procedures are available for review on ICSI's website at www.icsi.org.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Institute for Clinical Systems Improvement (ICSI). Menopause and hormone therapy (HT): collaborative decision-making and management. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2004 Oct. 57 p.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- ICSI pocket guidelines. April 2004 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2004. 404 p.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

PATIENT RESOURCES

The following is available:

- Menopause and hormone therapy (HT): Collaborative decision-making and management. Bloomington (MN): Institute for Clinical Systems Improvement, 2005 Aug.

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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